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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,270	SPADAFORA ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-9 and 12* is/are pending in the application.

4a) Of the above claim(s) *6* is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *3-5,7-9 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/24/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application was filed on 06/24/2004. Claims 1-11 are pending.

Applicant's amendment filed on 05/06/2009, amended claims 3, 5, 8, and cancelled claims 1-2, 10-11. Applicant's amendment also added new claim 12.

Currently, claims 3-9, and 12 are pending.

Election/Restrictions

Applicant's arguments regarding the restriction into two groups I and II are persuasive, and the restriction requirement is herein withdrawn.

Applicant's arguments regarding species election requirement are not persuasive. Applicant's election with traverse efavirenz as the species in the reply filed on 04/22/2009 is acknowledged. It is pointed out that the species lack the same structure and will have different properties such as binding affinities, solubilities, modes of operation etc. For example, the diazepine compound, nevirapine, is structurally different from efavirenz and will have different properties. Thus the species are patentably distinct. A reference to one species will not be the same for other species. and the corresponding diversity in the field of search for each. Although, the search for the species is overlapping, the search would not be coextensive. An unburden search and examination burden is imposed on the office. Therefore, restriction for examination purposes as indicated is proper. The species election requirement is made final. Claim 6 is withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected species.

Claims 3-5, 7-9, and 12 are examined herein so far as they read on the elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-5, 7-9, and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to counteract the loss of cellular differentiation and to treat cell proliferation in particular tumor and non tumor pathologies comprising administering an effective amount of efavirenz, does not reasonably provide enablement for a method to counteract the loss of cellular differentiation and to treat cell proliferation in any tumor and any non tumor pathologies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention **commensurate in scope** with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without **undue experimentation**. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method to counteract the loss of cellular differentiation and to treat cell proliferation in any tumor and non tumor pathologies comprising administering an effective amount of efavirenz. The nature of the invention is complex in that it encompasses the treatment of cell proliferation in any tumor and non tumor pathologies.

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass treatment of cell proliferation **in any** number of tumor and non tumor pathologies.

(3). Guidance of the Specification / (4). Working Examples::

The specification does not provide any guidance as to how one would administer the claimed instant compound to a subject and treat cell proliferation in any tumor and non tumor pathologies **in general**.

Applicant provides in the specification on pages 16-17, Examples 7-8, *in vitro* data, for NIH/3T3 embryo fibroblasts, F9 teratocarcinoma cells, in murine cell cultures, and in human HeLa adenocarcinoma, and osteosarcoma cells. Results in Fig. 8 show that exposure to efavirenz (broken line) decreases the rate of proliferation in NIH/3T3

embryo fibroblasts, F9 teratocarcinoma cell lines in a dose-dependent manner as compared to non-exposed cells (solid line). Results in Fig. 9 show that both HeLa (panels A) and Saos-2 (panels B) cell lines were sensitive to efavirenz and underwent a significant reduction in the rate of cell growth. Other than that no data is provided to counteract the loss of cellular differentiation and to treat cell proliferation in any tumor and non tumor pathologies in general as claimed comprising administering efavirenz.

(5). State of the Art:

While the state of the art is relatively high with regard to treating cell proliferation in specific tumor and non tumor pathologies, the state of the art with regard to counteract the loss of cellular differentiation and to treat cell proliferation in any tumor and non tumor pathologies comprising administering efavirenz in general is underdeveloped. In particular, for example there is no known anticancer agent which is effective to counteract the loss of cellular differentiation and to treat cell proliferation in any or all tumors/cancers. Carter, et al. (Chemotherapy of Cancer, 2nd ed., 1981) clearly teaches that for the forty known anticancer agents, none are effective against all cancers/to treat cell proliferation in any cancer (pages 362-365). There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers or cell proliferation in any tumor or non tumor pathology. This is true in part because for example, cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-I), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms.

Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect a single organ are often not generally treatable. For example, the main types of lung cancer are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. There is no such thing as a treatment of these generally because of their diversity. Thus, it is beyond the skill of oncologists today to get an agent to be effective against to counteract the loss of cellular differentiation and to treat cell proliferation in any tumor or non tumor pathologies generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. Thus, the existence of such a "silver bullet" for counteracting the loss of cellular differentiation and treating cell proliferation in any tumor and non tumor pathologies in general as claimed is contrary to our present understanding.

(6). Predictability of the Art:

The invention is directed to a method to counteract the loss of cellular differentiation and to treat cell proliferation in any tumor and non tumor pathologies in **general**. It is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). For example, diseases such as cancers are especially unpredictable due to their complex nature. Please refer to the discussion of Carter, et al. and the state of the art in (5) that shows the different treatments of cell proliferation in tumor pathologies/cancers.

The treatment of one type of tumor pathologies/cancer could not be necessarily the same for the other type.

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of skill in the art would have to first envision a tumor or non tumor pathology, a dosage for the compound, an appropriate pharmaceutical carrier, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for the compound. One would then need to test the compound in the model system to determine whether or not the compound is effective to counteract the loss of cellular differentiation and to treat cell proliferation in the particular tumor. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment of claimed disorders with the instant compound, one of skill in the art would have to then either envision a modification of the first pharmaceutical composition, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, and test the system again. In order to practice Applicant's invention, it would be necessary for one to conduct the preceding experimentation for each type of tumor/non tumor pathology because, as described by Carter, et al., there is no known drug effective for treating all types of tumors. Therefore, it would require **undue, unpredictable experimentation** to practice the claimed invention to counteract the loss of cellular differentiation and to treat cell proliferation in **any** tumor and non tumor pathologies in a human or animal subject by administering efavirenz.

Genetech, 108 F.3d at 1366 states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-5, 7-9, and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation, "derivatives of nevirapine, efavirenz, and delavirdine" in claims 3, and 7 render claims herein indefinite. The recitation, "derivatives of nevirapine, efavirenz, and delavirdine" are not clearly defined in the specification. Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to "derivatives of nevirapine, efavirenz, and delavirdine" herein. One of ordinary skill in the art would clearly recognize that "derivative" would read on any of those compounds having any widely varying groups that possibly substitute the compounds. Furthermore the derivates of those compounds recited in claims 3, and 7 are also not specified in any detail in the specification.

Any significant structural variation to a compound would be reasonably expected to alter its properties; e.g., physical, chemical, physiological effects and functions. Thus,

it is unclear and indefinite as to the "derivatives of nevirapine, efavirenz, and delavirdine" herein encompassed thereby.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 3-5, 7, and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by Murdaca et al. (AIDS, 2002, Jan, vol.16, No.2, PTO-1449).

Murdaca et al. discloses a method of treating Kaposi's sarcoma (tumor) comprising administering to a 37-year old man two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor, efavirenz. Murdaca et al. discloses that therapy was well tolerated and led to an increase in the CD4 T cell count, and thoracic-abdominal CT scan proved the absence of nodules in all viscera, confirming complete remission of KS. See the entire article. It is pointed out that administration of efavirenz in treating Kaposi's sarcoma inherently counteracts the loss of cellular differentiation and treats cell proliferation.

Thus, Murdaca et al. anticipate instant claims 3-5, 7, and 12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murdaca et al. as applied to claims 3-5, 7, and 12 above, and in view of Bahal et al. (US 6,235,733, PTO-892).

Murdaca et al. is applied as discussed above.

Murdaca et al. does not explicitly teach the employment of efaviranz in a pharmaceutical composition in the form of pills, suspensions or solutions.

Bahal et al. teaches palatable oral liquid pharmaceutical composition comprising efavirenz in a pharmaceutically acceptable carrier. See abstract ; column 1, lines 63-67; column 3, EXAMPLEs I-IV.

It would have been obvious to a person of ordinary skill in the art at the time of invention to employ efaviranz in a pharmaceutical composition in the form solutions for oral administration because Bahal et al. teaches the employment of efavirenz in pharmaceutically acceptable carrier in liquid form for oral administration. One of ordinary skill of art at the time of invention would have been motivated to employ efaviranz in a liquid pharmaceutical composition with carriers with reasonable

expectation of employing said pharmaceutical composition for treating Kaposi's sarcoma (tumor).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 7.30 am-3.30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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